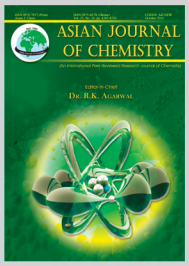
Asian Journal of Chemistry; Vol. 24, No. 2 (2012), 649-652

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



A Facile Synthesis of Dihydropyrimidine-Testosterone-Succinate

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(*Received*: 8 February 2011; *Accepted*: 12 October 2011) AJC-10499

In this study a new dihydropyrimidine-testosterone-succinate derivative was synthesized. The route involved the preparation of a dihydropyrimidine-testosterone derivative using the three-component system (testosterone, benzaldehyde and thiourea) in the presence of hydrochloric acid, followed by esterification of the dihydropyrimidine-testosterone derivative with succinic acid to form a dihydropyrimidine-testosterone-succinate derivative.

Key Words: Testosterone, Dihydropyrimidine, Benzaldehyde.

INTRODUCTION

Several dihydropyrimidine derivatives have been synthesized with a wide spectrum of biological actions[1], as antibacterials[2,3] and antivirals[4]. There are some reports of multicomponent reactions for synthesis of dihydropyrimidines, for example the work reported by Hantzsch[5], which described preparation of 1,4-dihydropyridine using a three-component coupling reaction (acetoacetic ester, benzaldehyde and ammonia or ammonium salts) in ethanol under reflux. Biginelli[6] has reported the synthesis of dihydropyrimidine derivatives using ethyl acetoacetate, benzaldehyde and urea. In addition, dihydropyrimidin-2(1*H*)-one was recently synthesized by use of the three component system urea/thiourea, ethyl acetoacetate and acetyl acetone in the presence of phosphorus pentoxide[7]. Additionally, in other work Surya and coworkers[8] achieved the synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones under solvent-free conditions using ruthenium(III) chloride as catalyst. In addition, Kappe and coworkers[9] have reported highly versatile solid-phase synthesis of biofunctional 4-aryl-3,4-dihydropyrimidines using resin-bound isothiourea building blocks and multidirectional resin cleavage. Another study reported by Shirinia and coworkers[10] showed that $Fe(HSO_4)_3$ can be an efficient catalyst for preparation of 3,4-dihydropyrimidin-2(1*H*)-ones using the three-component system β-keto ester, benzaldehyde and thiourea. Additionally, Salehia and coworkers[11] have reported the synthesis of dihydropyrimidinones using aldehyde derivatives, dicarbonyl compounds and urea or thiourea in presence of diammonium hydrogen phosphate. These experimental results show several procedures are available for synthesis of dihydropyrimidine derivatives by use of the Biginelli reaction. However, expensive reagents and special conditions are required. Recently, steroid-dihydropyrimidine was synthesized using hydrochloric acid as catalyst[12]. Therefore, in this study, our initial design included a facile synthesis of dihydropyrimidine-testosterone-succinate derivative (**6**) that contains, in the cyclopentane ring of the steroid nucleus, an arm with both ester and carboxyl functional groups. The route involves preparation of dihydropyrimidine-testosterone derivative (**4**) using, first, the three-component system testosterone, benzaldehyde and thiourea in the presence of hydrochloric acid as catalyst, followed by esterification of the steroid-dihydropyrimidine derivative with succinic acid and 1,3-dicyclohexylcarbodiimide to form **6**.

EXPERIMENTAL

General methods: Testosterone and the other compounds evaluated in this study were purchased from Sigma-Aldrich. Melting points were determined on an Electrothermal model 900. Ultraviolet spectroscopy (UV) was carried out in dry methanol on a Perkin-Elmer model 552 spectrophotometer and infrared spectra (IR) were recorded using KBr pellets on a Perkin-Elmer Lambda 40 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz, respectively, in DMSO-d_6, using TMS as internal standard. EI-MS spectra were obtained with

a Finnigan Trace GCPolaris Q spectrometer. Elemental analysis data were obtained by use of a Perkin-Elmer Ser.

Syntheses

10-Phenyl-1-hydroxy-11a,13a-dimethyl-1,2,3,3a,3b,4,5,7,9,10,11,11a,11b,12,13,13a-hexadecahydro-1*H*-7,9-diaza-indeno(5,4-a)anthracene-8-thione (4): A solution of 145 mg testosterone (0.50 mmol), 114 mg thiourea (1.49 mmol) and 60 µL benzaldehyde (1.62 mmol) in 10 mL of ethanol was stirred for 10 min at room temperature. Then 1 mL of hydrochloric acid was added and the mixture was stirred for 48 h at room temperature. The reaction mixture was evaporated to a smaller volume, diluted with water and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1) yielding 58 % of product **4** (**Scheme-I**). m.p. 180 ºC; UV (MeOH): λ_{max} (log ε) = 238 (3.18) nm; IR: (KBr, ν_{max}, cm^{-1}) 3,300, 1,630; ^{1}H NMR (300 HMz, DMSO-d_6) δ_H: 0.82 (s, 3H), 0.94-0.96 (m, 2H), 0.99(s, 3H), 1.02-1.36 (m, 4H), 1.44-1.93 (m, 7H), 2.12-2.41(m, 2H), 2.56 (d, 1H *J* = 18 Hz), 2.80 (d, 1H, *J* = 18 Hz), 3.66 (m, 1H), 4.91 (m, 1H), 5.99 (s, 1H), 7.20-7.28 (m, 3H), 7.30 (broad, 3H), 7.48 ppm. ^{13}C NMR (74.5 MHz, DMSO-*d*6) δ_C: 11.14 (C-24), 18.11 (C-23), 20.70 (C-20), 23.31 (C-14), 29.32 (C-7), 30.15 (C-13), 31.17 (C-19), 32.08 (C-18), 33.73 (C-6), 34.87 (C-9), 36.45 (C-21), 42.77 (C-11), 50.37 (C-8), 50.74 (C-10), 55.62 (C-15), 80.51 (C-12), 110.10 (C-16), 112.85 (C-5), 128.40 (C-29), 128.90 (C-28, C-30), 129.60 (C-27, C-31), 138.72 (C-26), 142.02 (C-4), 150.04 (C-17), 166.04 (C-2), 171.85 (C-36), 173.40 ppm. MS (70 eV): m/z = 434.40 [M^+], 324.5, 267.43, 132.2. Anal. calcd. (%) for. $C_{27}H_{34}N_2OS$: C, 74.61; H, 7.88; N, 6.45; S, 7.38. Found (%): C, 74.58; H, 7.84.

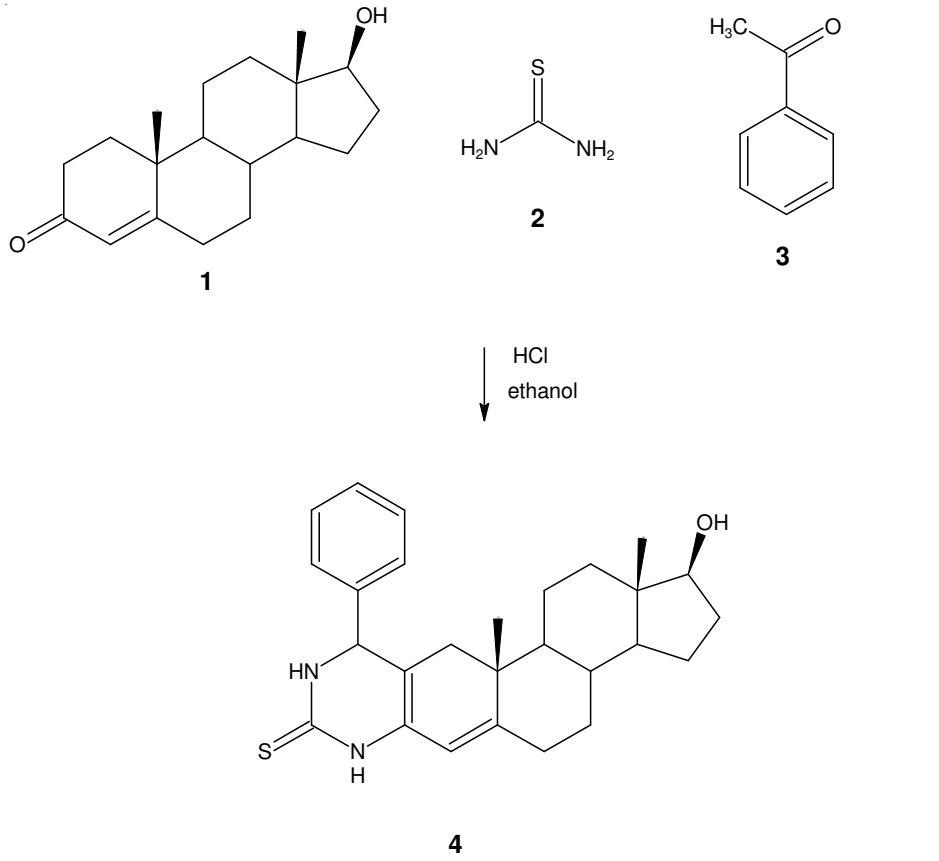
Succinic acid mono-(phenyl)-11a,13a-dimethyl-8-thioxo-2,3,3a,3b,4,5,7,8,9,10,11,11a,11b,12,13,13a-hexadecahydro-1*H*-7,9-diaza-indeno[5,4-a]anthracen-1-yl)ester (6): The compound **4** (150 mg, 0.34 mmol) was added to a solution of 80 mg succinic acid (0.68 mmol) and 106 mg 1,3-dicyclohexylcarbodiimide (0.50 mmol) in 15 mL acetonitrile-water (3:1) and 69 mg *p*-toluenesulfonic acid monohydrate (0.36 mmol) was added and the mixture was stirred at room temperature for 72 h. The solvent was then removed under vacuum and the crude product was purified by crystallization from methanol:hexane:water (3:2:1) yielding 64 % of product **6** (**Scheme-II**). m.p. 218-220 ºC; UV (MeOH): λ_{max} (log ε) = 223 (3.20) nm; IR (KBr, ν_{max}, cm^{-1}): 3,306, 1,625, 1,550; ^{1}H NMR (300 HMz, DMSO-d_6) δ_C; 0.80 (s, 3H), 0.88 (m, 1H), 0.99 (s, 3H), 1.04-1.19 (m, 3H), 1.39-1.92 (m, 8H), 2.13-2.43 (m, 3H), 2.55 (m, 2H) 2.57 (m, 2H), 2.61 (m, 1H), 2.84(m, 1H), 4.65 (m, 1H), 4.80 (m, 1H) 5.66 (s, 1H), 7.18-7.50 (m, 5H), 8.22 (broad, 3H) ppm. ^{13}C NMR (74.5 MHZ, DMSO-d_6) δ_C; 12.08 (C-24),18.11 (C-23), 20.56 (C-20), 24.19 (C-14), 27.36 (C-23), 29.32 (C-7), 29.36 (C-34, C-35), 31.71 (C-19), 32.08 (C-18), 33.73 (C-6), 34.87 (C-9), 35.68 (C-21), 42.64 (C-11), 50.30 (C-8), 51.61 (C-10), 65.62 (C-15), 82.43 (C-12), 110.10 (C-16), 112.85 (C-5), 128.40 (C-31), 128.90 (C-30, C-32), 129.60 (C-29, C-33), 138.71 (C-28), 142.02 (C-4), 150.04 (C-17), 166.04 (C-2), 171.80 (C-36), 173.40 (C-26) ppm. MS (70 eV): m/z = 534.10 [M^+], 396.6, 325.5, 217.31. Anal. calcd. (%) for $C_{31}H_{38}N_2O_4S$: C, 69.63; H, 7.16; N, 5.24; S, 6.00. Found (%): C, 69.58; H, 7.12.

RESULTS AND DISCUSSION

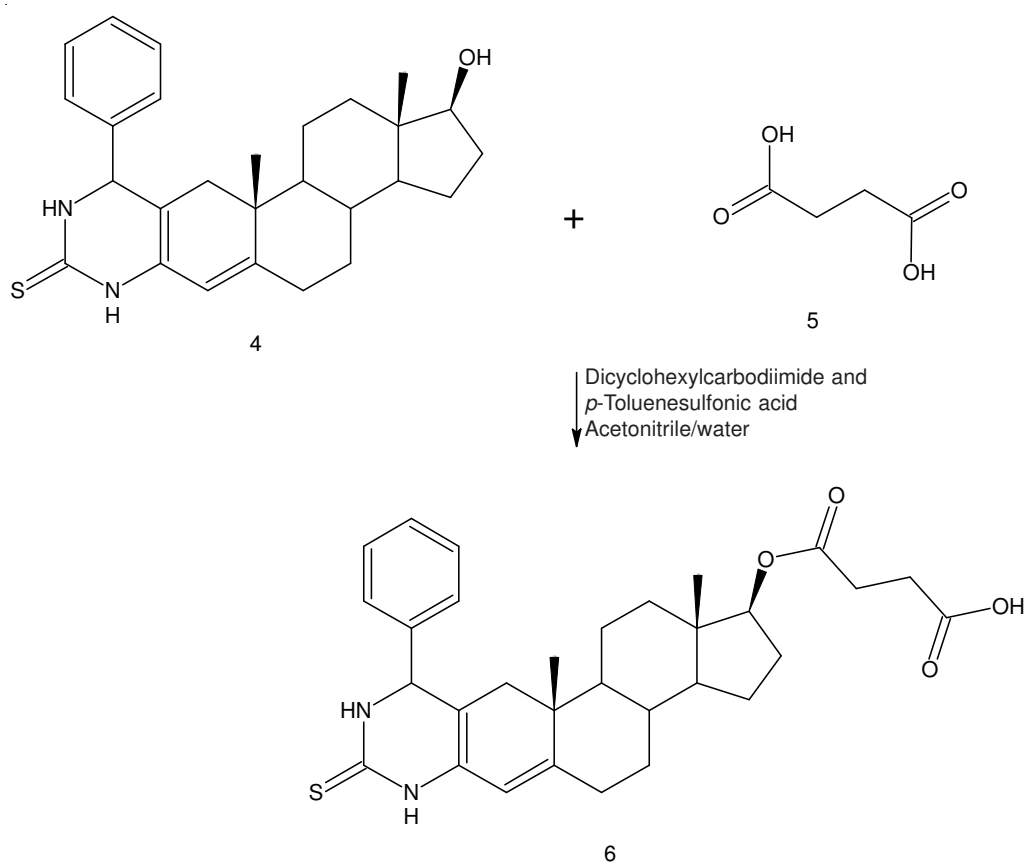
There are many procedures for formation of dihydropyrimidine derivatives which are available in the literature. The most widely practiced methods employ boric acid[13], silica sulfuric acid[14], poly-(4-vinylpyridine-co-divinylbenzene)-Cu(II) complex[15], H_2SO_4[16], silica triflate[17] and phosphorus pentoxide[7]. Nevertheless, despite their wide scope, these procedures suffer from several drawbacks. Some reagents are of limited stability and preparation can be dangerous. Therefore, in this work we report a straightforward route for synthesis of dihydropyrimidine-testosterone-succinate derivative. The first step involves preparation of dihydropyrimidine-testosterone derivative (**4**) using the three-component system testosterone, benzaldehyde and thiourea in presence of hydrochloric acid as catalyst (**Scheme-I**). The ^{1}H NMR spectrum of the dihydropyrimidine-testosterone derivative shows signals at 0.82 and 0.99 ppm for methyl groups present in the heterocyclic rings and at 4.91 ppm for CH involved in the pyrimidine ring; at low field there are several chemical shifts (7.20-7.28 and 7.48 ppm) corresponding to protons in the aromatic ring. Finally, the spectrum contains a signal at 7.48 ppm for the NH (pyrimidine ring) and OH.

The ^{13}C NMR spectrum contains peaks at chemical shifts of 11.14 and 18.11 ppm for the carbons of the methyl groups present in the heterocyclic ring. The chemical shifts of methylene joined to the pyrimidine ring are at 110.10 (C-C=C) and 142.02 ppm (C=C-N). Downfield there are several signals (128.40-139.72 ppm) corresponding to the carbons of the aromatic ring. Finally, in the mass spectrum the molecular ion is atm/z = 434.40 ([M + H]$^+$), which confirms the structure of **4**. The second step involves esterification of the hydroxyl group of the dihydropyrimidine-testosterone derivative by reaction of **4** with succinic acid (**5**). It is important to mention that diverse reagents are available for producing ester derivatives[18,19]; nevertheless, most conventional methods have found only limited use for this purpose. During recent years, carbodiimides and, especially, dicyclohexylcarbodiimide (DCC) have attracted increasing attention as condensing agents in ester synthesis[20,21]. Nevertheless, it is important to mention that when dicyclohexylcarbodiimide is used as condensing agent in esters synthesis, yields of the esters are often unsatisfactory because of formation of the N-acylurea derivative as by-product. Some reports reveal that addition of a catalytic amount of a strong acid to the esterification reaction in the presence of dicyclohexylcarbodiimide considerably increases the yield of esters and reduces the formation of the N-acylurea compound[22]. For this reason, esterification of the hydroxyl group of **4** with **5** in the presence of dicyclohexylcarbodiimide and *p*-toluenesulfonic acid (**Scheme-II**) was used to increase the yield of the dihydropyrimidine-testosterone-succinate derivative (**6**).

The ^{1}H NMR spectrum of **6** shows signals at 0.80 and 0.99 ppm for methyl groups present in the heterocyclic ring and at 4.80 ppm for CH in the pyrimidine ring. In addition, at low field there are several signals (7.18-7.50 ppm) corresponding to protons in the aromatic ring. Finally, the spectrum contains a signal with a chemical shift of 8.22 ppm for NH (pyrimidine ring) and CO_2H.



Scheme-I: Synthesis of dihydropyrimidine-testosterone derivative (**4**) using the three-component system testosterone, benzaldehyde and thiourea in the presence of hydrochloric acid as catalyst



Scheme-II: Synthesis of dihydropyrimidine-testosterone-succinate (**6**). Reaction between the compound 4 with succinic acid (**5**) using 1,3-dicyclohexylcarbodiimide as catalyst in acetronitrile:water

The ^{13}C NMR spectrum of 6 contains peaks at chemical shifts of 12.08 and 18.11 ppm for the carbons of the methyl groups present in the heterocyclic ring. The chemical shifts of methylene joined to the pyrimidine ring are at 110.10 (C=C-C) and 142.02 ppm (N-C=C). At low field there are several signals (128.40-138.71 ppm) corresponding to the carbons of the aromatic ring. Several chemical shifts at 171.80 (CO_2H); at 166.04 ppm (N-C=S, pyrimidine ring) and 173.40 ppm (O-C=O) are also found. Finally, in the mass spectrum the molecular ion is at m/z = 534.10 ($[M + H]^+$), which confirms the structure of **6**.

Conclusion

In this study we report an efficient and simple method for synthesis of the dihydropyrimidine-testosterone derivative (**4**), using a multi-component system in the presence of hydrochloric acid as catalyst. It is important to mention that this method is highly versatile and the yield is good. In addition, esterification of the dihydropyrimidine-testosterone derivative using succinic acid in the presence of 1,3-dicyclohexylcarbodiimide and *p*-toluenesulfonic acid is a good system for increasing the yield of **6**.

ACKNOWLEDGEMENTS

One of the authors (LFV) is grateful to Gloria Velazquez Zea for valuable comments on the manuscript.

REFERENCES

1. G.C. Cheng, *Prog. Med. Chem*., **6**, 67 (1969).
2. R. Mishra, B. Mishra and H. Moorthy, *Trends Appl. Sci. Res*., **3**, 203 (2008).
3. A.K. Padhy, M. Bardhan and C.S. Panda, *Indian J. Chem*., **42B**, 910 (2003).
4. S.G. Vishnevskii, V.V. Pirozhenko, N.P. Chentsova, S.V. Antonenko E.V. Barbasheva, E.V. Grin, M.G. Lyul'chuk, A.E. Sorochinskii, G.Y. Remennikov, A.I. Puik and V.P. Kukhar, *Pharm. Chem. J*., **28**, 44 (1994).
5. A. Hantzsch, *Ann. Chem*., **215**, 1 (1892).
6. C.O. Kappe, *Acc. Chem. Res*., **33**, 879 (2000).
7. M.B. Deshmukh, V. Prashant, P.V. Anbhule, S.D. Jadhav, A.R. Mali, S.S. Jagtap and S.A. Deshmukh, *Indian J. Chem*., **46B**, 1545 (2007).
8. K.D. Surya and R.A. Gibbs, *Synthesis*, 1748 (2005).
9. C.O. Kappe, *Bioorg. Med. Chem. Lett*., **10**, 49 (2000).
10. F. Shirinia, M.A. Zolfigolb and A.R. Abria, *J. Iran Chem. Soc*., **5**, 96 (2008).
11. P. Salehia, M. Dabirib, A.R. Khosropour and P. Roozbehniya, *J. Iran. Chem. Soc*., **3**, 98 (2006).
12. L. Figueroa-Valverde, F. Díaz-Cedillo and A. Camacho-Luis, *Monatsh. Chem*., **141**, 75 (2009).
13. S. Tu, F. Fang, C. Miao, H. Jiang, Y. Feng, D. Shi and X. Wang, *Tetraheron Lett*., **44**, 6153 (2003).
14. P. Salehi, M. Dabiri, M.A. Zolfigol and M.B. Fard, *Tetrahedron Lett*., **44**, 2889 (2003).
15. R.V. Yarapathi, S. Kurva and S. Tammishetti, *Catal. Commun*., **5**, 511 (2004).
16. J.C. Bussolari and P.A. McDonnell, *J. Org. Chem*., **65**, 6777 (2000).
17. F. Shirini, K. Marjani and H.T. Nahzomi, *Arkivoc*, 51 (2007).
18. R.K. Crossland and K.L. Servis, *J. Org. Chem*., **35**, 3195 (1970).
19. H.P. Zhu, F. Yang, J. Tang and M.Y. He, *Green Chem*., **5**, 38 (2003).
20. F. Kurzer and K. Douraghi-Zadeh, *Chem. Rev*., **67**, 107 (1967).
21. E. Felder, U. Tiepolo and A. Mengassini, *J. Chromatogr*., **82**, 291 (1973).
22. K. Holmberg and B. Hansen, *Acta Chem. Scand*., **B33**, 410 (1979).